

Predictors of impaired endothelial function in obstructive sleep apnea syndrome

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Submitted: 2014-02-20 *Accepted:* 2014-03-15 *Published online:* 2014-05-05

Key words: **obstructive sleep apnea syndrome; polysomnography; endothelial dysfunction; reperfusion hyperaemia index; baroreflex sensitivity**

Neuroendocrinol Lett 2014; **35**(2):142-148 PMID: 24878978 NEL350214A06 © 2014 Neuroendocrinology Letters • www.nel.edu

Abstract

OBJECTIVES: Obstructive sleep apnea syndrome (OSA) is associated with increased cardiovascular morbidity and mortality. Endothelial dysfunction (ED), accelerated atherosclerosis and autonomic dysfunction might be the key players responsible for development of vascular diseases in patients with OSA. In a population with suspected OSA and low burden of cardiovascular risk factors, we therefore aimed to investigate the association between potential cardiovascular risk factors including OSA-specific indices, ED and autonomic activity.

METHODS: ED was investigated using reperfusion hyperaemia index (RHI). OSA was assessed using standard polysomnography, autonomic activity was assessed using baroreflex sensitivity (BRS).

RESULTS: We enrolled 31 patients (42.1±11.7 years) with OSA. Significant inverse correlation was found between RHI and apnea-hypopnea index (AHI) ($r=-0.550$, $p=0.001$) and between RHI desaturation index ($r=-0.533$, $p=0.002$). Positive correlation was found between RHI and minimal nocturnal oxygen saturation ($r=0.394$, $p=0.028$). In a multiple regression model AHI was the only significant variable to predict RHI ($\beta=-0.522$, $p=0.003$). We found no correlation between RHI and BRS. RHI in the population with severe OSA (AHI above 30) was significantly lower than RHI in the rest of the population ($p=0.012$).

CONCLUSION: AHI was the only significant independent predictor of impaired endothelial function as expressed by RHI. RHI showed no association with BRS in patients with OSA.

Abbreviations:

OSA - obstructive sleep apnea syndrome
ED - endothelial dysfunction
RHI - reperfusion hyperaemia index
BRS - baroreflex sensitivity
AHI - apnea-hypopnea index
DI - desaturation index
PAT - peripheral arterial tonometry

TG - triglyceride
LDL - low density lipoprotein
HDL - high density lipoprotein
BMI - body mass index
AI - arousal index
ESS - epworth sleepiness scale
FMD - flow-mediated dilatation
IQR - interquartile range

INTRODUCTION

Obstructive sleep apnea syndrome (OSA) is a highly prevalent disorder accounting for 1–5% of adult male and 1–2% of adult women population (Young *et al.* 2002). OSA is associated with increased cardiovascular morbidity and mortality. It is associated with cardiovascular diseases including hypertension, ischemic heart disease and stroke (Shahar *et al.* 2001). Potential pathophysiologic mechanisms linking OSA with genesis of vascular diseases are endothelial dysfunction (ED), sympathetic activation, oxidative stress, metabolic dysregulation and changes of coagulation and inflammation (Lopez-Jimenez *et al.* 2008). Accelerated atherosclerosis might be one of the most important mechanisms responsible for development of vascular disorders in patients with OSA (Lévy *et al.* 2009). ED is an initial process and a key component of atherogenesis (Bonetti *et al.* 2003). Association of ED with OSA has been described in several studies (Kohler *et al.* 2008). ED is present also in patients with OSA who do not suffer any other vascular disease (Ip *et al.* 2004). ED in patients with OSA seems to be linked to the repetitive sleep apnea-associated hypoxemia-reoxygenation (Nieto *et al.* 2004). Oxidative stress is considered to be one of the most important mechanisms in the pathogenesis of ED (Victor *et al.* 2009). Development of ED is associated also with several other cardiovascular risk factors such as male sex, hypertension, diabetes mellitus, hyperlipidemia, obesity and smoking. Risk of development of ED seems to be increased with the interaction of more risk factors (Hamburg *et al.* 2008). ED is associated with increased cardiovascular morbidity. Several studies have proven prognostic value of ED and also role of ED as an independent predictor of adverse cardiovascular events (Gokce *et al.* 2002).

Another important mechanism reported in the pathophysiology of OSA is sympathetic overactivation. Increased sympathetic drive probably results from recurrent nocturnal respiratory events. Sympathetic overactivity is present also in subjects with OSA without any other vascular disease and is present also during daytime (Narkiewicz *et al.* 1998). Reactive oxygen species that play a crucial role in the development of ED has been shown to be involved in activation of the sympathetic nervous system (Gao *et al.* 2004). Interaction between the sympathetic and endothelial function in cardiovascular regulation is described in animal studies (Sartori *et al.* 2005). Despite limited data from human studies exist, an acute increase in sympathetic activity has been shown to cause an impairment of endothelial function. Hijmering shows that sympathetic stimulation evoked by baroreceptor unloading markedly reduces flow-mediated vasodilatation (FMD) (Hijmering *et al.* 2002). Decreased BRS is a feature of OSA (Cortelli *et al.* 2012). Decreased BRS is present in several cardiovascular diseases and

predicts adverse cardiovascular events (De Ferrari *et al.* 2007).

The aim of this study was to explore predictors of impaired endothelial function, including decreased BRS, in population of patients with suspected OSA without any overt cardiovascular risk factors.

MATERIAL AND METHODS

Study population

The subjects were recruited from the population of patients examined in the sleep laboratory of the 1st Department of Neurology, Bratislava, Slovakia with suspected diagnosis of OSA from November 2011 to January 2013. Exclusion criteria were previous treatment for OSA, history of hypertension, cardiovascular disease, diabetes mellitus, renal disease, other chronic diseases or medications and smoking habit. This study was approved by the institutional ethics committee. All patients provided informed consent.

Polysomnography

Subjects underwent overnight polysomnography in the sleep laboratory (Alice 5, Philips-Respironics, Netherlands) as previously described (Schiza *et al.* 2010). Polysomnography included channels for electroencephalogram, electrooculogram, chin electromyogram, finger arterial oximetry, electrocardiogram, tibialis electromyogram and body position. Breathing effort was monitored with a chest and abdominal belt and airflow was monitored by a nasal cannula. Recordings were scored manually. Sleep parameters and respiratory events were scored according to standardized criteria (American Academy of Sleep Medicine 2007).

Biochemical analysis

Biochemical blood tests were performed in the morning after polysomnography. Blood samples were obtained while the subjects were in the fasting state. Samples were processed in local hospital laboratory and included.

Measurement of endothelial function

Measurement of reactive hyperemia index (RHI)-parameter for endothelial function, was performed day after polysomnography. Measurement was performed using the EndoPAT 2000 device (Itamar Medical, Caesarea, Israel). Peripheral arterial tonometry (PAT) finger probes were placed on the index finger of both hands. Protocol consisted of a 5 minutes baseline measurement followed by 5 minutes of brachial artery occlusion induced by inflating the cuff. After 5 min, the cuff was deflated and the PAT signal was recorded for a further 5 minutes. Measures were calculated using an automated algorithm and were performed according to the manufacturer's instructions (Axtell *et al.* 2010). Assessment of endothelial function was performed at approximately 1:00 to 3:00 PM.

Measurement of baroreflex sensitivity

Baroreflex sensitivity was assessed immediately after assessment of endothelial function using Finometer device (FMS, Finapres Medical Systems BV, Amsterdam, Netherlands) as previously described (Sykora *et al.* 2009).

Statistical analysis

Continuous variables were expressed as means \pm standard deviation or median, interquartile range, minimal and maximal values. Categorical variables were expressed as numbers and proportions (%). Normal distribution of variables was investigated visually by histograms and by Kolmogorov-Smirnov normality test. Pearson or Spearman correlation coefficients were used to determine relationships between RHI and cardiovascular risk parameters including BRS. Stepwise multiple linear regression analysis was used to identify factors that contributed to RHI. To compare RHI in populations with different severity of OSA we used the

Tab. 1. Baseline characteristics.

Variable	n=31
Male sex	26 (83.9%)
Age (years)	42.06 \pm 11.67
RHI	2.16 \pm 0.57
BRS (ms/mmHg)	7.80, 9.60 (3.10–26.90)
AHI (n/h)	24.7, 41.4 (0–113.2)
DI (n/h)	15.10, 44.3 (0.2–119.9)
AI (n/h)	17.60, 39.60 (5–241)
Average sat (%)	91.58 \pm 5.38
Minimal sat (%)	80.90 \pm 15.51
ESS	6.00, 6.00 (2.00–15.00)
Glycaemia (mmol/L)	5.38 \pm 0.78
Leucocyte count (x10 ⁹ /L)	6.91 \pm 2.05
TAG (mmol/L)	1.80 \pm 1.05
Total cholesterol (mmol/L)	4.96 \pm 1.35
LDL (mmol/L)	3.71 \pm 1.26
HDL (mmol/L)	1.18 \pm 0.30
Height (cm)	175.35 \pm 13.62
BMI (kg/m ²)	30.25 \pm 5.75
Weight (kg)	95.06 \pm 18.37
Neck circumference (cm)	41.52 \pm 3.97
Systolic BP (mmHg)	129.84 \pm 12.75
Diastolic BP (mmHg)	76.29 \pm 10.49

BRS - baroreflex sensitivity, RHI - reperfusion hyperaemia index, TAG - triglyceride, LDL - low density lipoprotein, HDL - high density lipoprotein, BP - blood pressure, AHI - apnea-hypopnea index, DI - desaturation index, AI - arousal index, BMI - body-mass index, ESS - Epworth sleepiness scale, sat - saturation of blood with oxygen

Mann-Whitney test. All tests were 2 sided. The *p*-values <0.05 were considered statistically significant. The analyses were assessed with SPSS version 18 (SPSS Inc., Chicago, USA).

RESULTS

Baseline characteristics of the population are shown in Table 1. The average age was 42.06 \pm 11.67 years, 83.9% of the population were male. Median of apnea-hypopnea index (AHI) in the population was 24.7, median of desaturation index (DI) 15.1 and mean average saturation of blood with oxygen was 91.58%. Severe sleep apnea (AHI \geq 30) was present in 14 patients (45.2%), moderate sleep apnea (AHI 15–30) in 9 patients (29%) and no or mild sleep apnea (AHI below 15) in 8 patients (25.8%). Average reperfusion hyperaemia index (RHI) was 2.16 \pm 0.57. Inverse relationship was found between RHI and AHI ($r=-0.550$, $p=0.001$) and also RHI and desaturation index (DI) ($r=-0.533$, $p=0.002$). Relationship was found between RHI and minimal nocturnal saturation of blood with oxygen ($r=0.394$, $p=0.028$). No significant correlation was found between RHI and age, glycaemia, leucocyte count, serum levels of total cholesterol, triglyceride (TG), low density lipoprotein

Tab. 2. Correlation between RHI and baseline characteristics.

Variable	r-value
Age	-0.198
AHI	-0.550***
DI	-0.533**
AI	-0.178
Average sat	0.307
Minimal sat	0.394*
ESS	-0.169
BRS	0.259
Glycaemia	-0.342
Leucocyte count	-0.206
TAG	-0.090
Total cholesterol	-0.096
LDL	-0.124
HDL	0.120
BMI	-0.263
Neck circumference	-0.271
Systolic BP	-0.070
Diastolic BP	-0.006

BRS - baroreflex sensitivity, TAG - triglyceride, LDL - low density lipoprotein, HDL - high density lipoprotein, BP - blood pressure, AHI - apnea-hypopnea index, DI - desaturation index, AI - arousal index, BMI - body-mass index, ESS - Epworth sleepiness scale, sat - saturation of blood with oxygen, * $p<0.05$, ** $p<0.01$, *** $p<0.001$

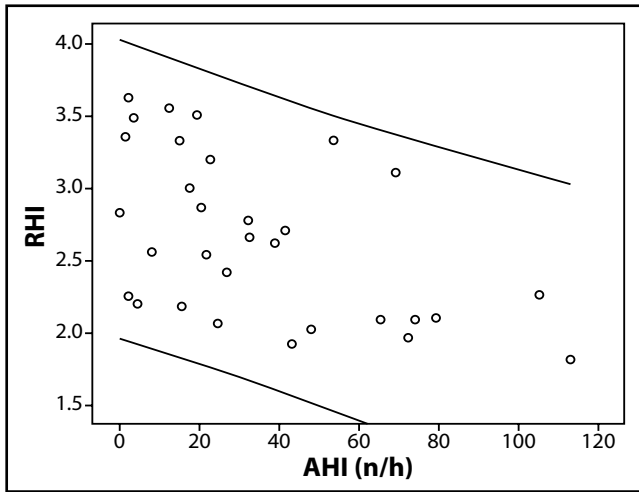


Fig. 1. Association between RHI and AHI. $r=-0.550$, $p=0.001$ (RHI - reperfusion hyperaemia index, AHI - apnea-hypopnea index).

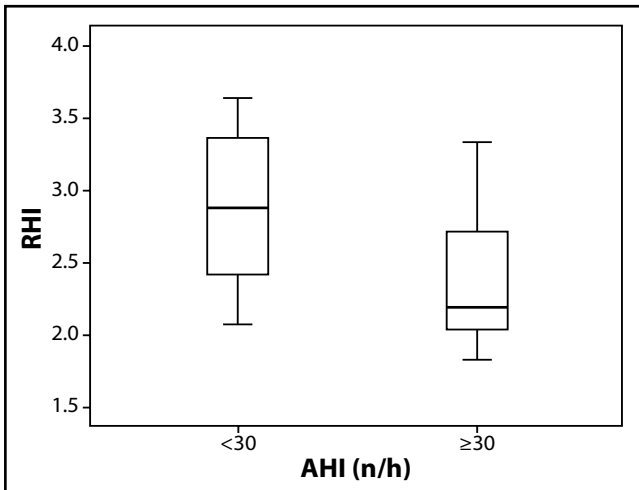


Fig. 2. RHI in the population with severe OSA (AHI above 30) and in the rest of the population. $RHI(<30)=2.38\pm0.55$ vs $RHI(\geq30)=1.89\pm0.48$ ($p=0.012$). (RHI - reperfusion hyperaemia index, AHI - apnea-hypopnea index).

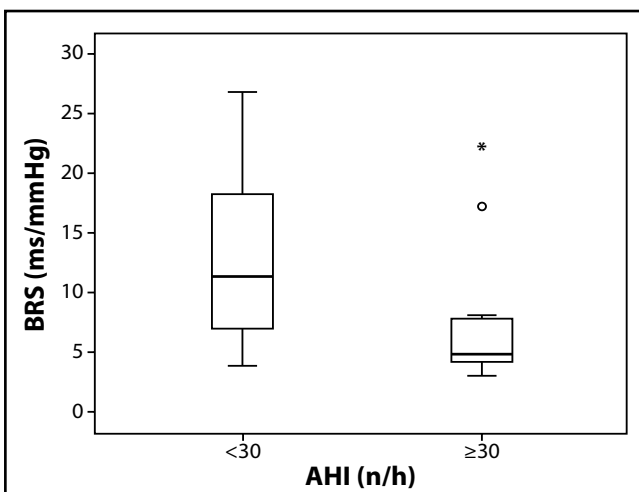


Fig. 3. BRS in the population with severe OSA (AHI above 30) and in the rest of the population. Median $BRS(<30)=11.40$ ms/mmHg vs median $BRS(\geq30)=4.85$ ms/mmHg ($p=0.012$), (BRS - baroreflex sensitivity, AHI - apnea-hypopnea index).

(LDL), high density lipoprotein (HDL), body mass index (BMI), blood pressure, average nocturnal saturation of blood with oxygen, arousal index (AI), daytime sleepiness (ESS) and baroreflex sensitivity (BRS) ($r=0.259$, $p=0.159$). Stepwise multiple linear regression analysis was performed to identify significant contributing factors for RHI among independent variables. AHI ($\beta=-0.522$, $p=0.003$) was the only significant variable to determine RHI. Correlation between AHI and RHI is shown in Figure 1. Average RHI in the population with severe OSA (AHI above 30) was 1.89 ± 0.48 , which was significantly lower ($p=0.012$) than RHI in the rest of the population (AHI below 30), where the average value was 2.38 ± 0.55 . Values of RHI in population with severe OSA and in the rest of the population are shown in Figure 2. Median value of BRS in the population with severe OSA (AHI above 30) was 4.85 ms/mmHg, IQR 3.60 (3.10–22.20), which was significantly lower ($p=0.012$) than BRS in the rest of the population (AHI below 30), where median value was 11.40 ms/mmHg, IQR 13.00 (3.90–26.90). Values of BRS in population with severe OSA and in the rest of the population are shown in Figure 3.

DISCUSSION

In the absence of classical cardiovascular risk factors we found AHI to be the only significant variable to determine impaired endothelial function in a population with OSA. Although both RHI and BRS were significantly lower in the population with severe OSA as compared to the rest of the population, RHI showed no association with BRS in our series.

Several studies support influence of vascular risk factors on endothelial function. Results from Framingham study suggest a significant inverse relationship between PAT ratio and multiple vascular risk factors. In population of 1957 participants PAT ratio was inversely associated with male sex, body mass index, ratio of total to HDL cholesterol, diabetes mellitus, smoking and lipid-lowering therapy (Hamburg *et al.* 2008). Participants with a wide spectrum of cardiovascular risk factors were included in previous study. In a population of 54 healthy participants without known cardiovascular disease PAT hyperemic response was significantly associated with age, triglycerides, fasting glucose, HDL, waist to hip ratio, waist circumference and visceral adiposity. In multivariate regression analyses, triglyceride level remained only significant determinant of PAT hyperemic response (Fitch *et al.* 2011).

None of these studies considered sleep disordered breathing as a cardiovascular risk factor and possible predictor of endothelial dysfunction. Sleep disordered breathing should be obviously considered as a vascular risk factor. Impairment of endothelium-dependent vasodilatation has been observed in patients with OSA who were free of any other overt cardiovascular disease (Kato *et al.* 2000). Correlation between severity of

endothelial dysfunction, assessed by plethysmography or FMD, and the severity of OSA has been reported previously (Nieto *et al.* 2004). Multiple studies searched for predictors of decreased FMD in OSA patients. In a study of 1037 participants from Sleep Heart Health/ Cardiovascular Health Study cohort revealed that sleep apnea measures were associated with the percentage of FMD. These associations were weakened after adjustment for other cardiovascular risk factors. (Nieto *et al.* 2004). Kraiczi reports correlation of FMD characteristics with minimum oxygen saturation. In a cohort of twenty subjects without regular medication and without known cardiovascular disease, percentage of sleep time spent in hypoxemia predicted reduced endothelium-dependent dilatatory capacity of the brachial artery after adjustment for age ($p < 0.05$) (Kraiczi *et al.* 2001). Lowest oxygen saturation was described as a significant predictor for endothelial dysfunction also in more recent studies. In multivariate analysis, the lowest oxygen saturation was a significant determinant for FMD ($\beta = 0.25$, $p < 0.01$) in a population of 83 OSA patients (Chung *et al.* 2010). Another authors described, in a cohort of 29 normotensive men, significant inverse relationship between FMD and AHI adjusted for age and body mass index ($\beta = -0.05$, $p < 0.001$) (Bayram *et al.* 2009). Ip describes, in a study of 40 patients, negative correlation of FMD with AHI ($r = -0.655$, $p < 0.001$), time with oxygen saturation $< 90\%$ ($r = -0.620$, $p < 0.001$), arousal index ($r = 0.516$, $p = 0.001$) and positive correlation with minimum oxygen saturation ($r = 0.577$, $p < 0.001$). FMD was not significantly correlated with Epworth Sleepiness Scale score, age, BMI, serum glucose, cholesterol levels and blood pressure. Stepwise multiple linear regression analysis showed, that AHI and age were significant determinants of baseline FMD, independent of other vascular risk factors (Ip *et al.* 2004).

Predictors of impaired reperfusion hyperaemia using PAT are not so commonly studied as predictors of impaired FMD. Itzhaki describes inverse correlation between morning RH-PAT index and AHI ($r = -0.42$, $p < 0.001$), history of hypertension or cardiovascular disease ($r = -0.60$, $p < 0.02$) and for patients without such history ($r = -0.26$, $p < 0.06$). In the same study no correlation between evening RH-PAT and AHI or minimum oxygen saturation and evening RH-PAT was found (Itzhaki *et al.* 2005). The same authors described diurnal variations in endothelial function only in sleep apnea patients. Lower morning and higher evening RH-PAT index were described. Morning RH-PAT index values, but not the evening values, were associated with severity of OSA (Itzhaki *et al.* 2005). In our study, endothelial function was measured in the early afternoon hours, when it should theoretically exhibit average values.

Our findings, in a group of 31 patients with suspected OSA with low-risk cardiovascular profile, correspond with the literature. Inverse significant correlation

was found between RHI and AHI ($r = -0.550$, $p = 0.001$), between RHI and desaturation index ($r = -0.533$, $p = 0.002$). Positive correlation was found between RHI and minimal nocturnal saturation of blood with oxygen ($r = 0.394$, $p = 0.028$). In stepwise multiple linear regression analysis AHI was the only significant variable to determine RHI ($\beta = -0.522$, $p = 0.003$). RHI in the population with severe OSA (AHI above 30) was significantly lower than RHI in the rest of the population ($p = 0.012$). Similar findings were described previously. Significantly lower morning RH-PAT were present in a group with severe OSA than in the controls ($p < 0.003$) and than in the group with mild OSA ($p < 0.009$) (Itzhaki *et al.* 2005). In FMD studies, the severe OSA group showed lower FMD than the control group (Bayram *et al.* 2009).

We found no significant correlation between RHI and age, glycaemia, leucocytes count, serum levels of total cholesterol, triglyceride (TG), low density lipoprotein (LDL), high density lipoprotein (HDL), body mass index (BMI), blood pressure, average nocturnal saturation of blood with oxygen, arousal index (AI), daytime sleepiness (ESS) and baroreflex sensitivity (BRS). Inability to find any other predictors of decreased RHI can be theoretically explained by the fact, that our population had low vascular risk factors burden. Minimum of the considered risk factors exceeded reference values and sleep disordered breathing might apparently be most important cardiovascular risk factor in such a population.

This is the first study so far to look for possible association between endothelial dysfunction and impaired cardiovascular autonomic nervous system regulation (represented by BRS) in OSA patients. Impaired endothelial function and reduced BRS have been described in patients with OSA and both parameters are markers of increased cardiovascular risk (Kohler *et al.* 2008). Literature describes a kind of functional antagonism between sympathetic nervous system and function of endothelial cells, that could be necessary to maintain appropriate blood vessel tone. Impaired function of sympathetic nervous system and endothelial dysfunction may result in disruption of this functional antagonism and development of vascular disease (Harris & Matthews 2004). Although both RHI and BRS were significantly lower in the population with severe OSA than in the rest of the population ($p = 0.012$ in both cases), we failed to find any significant association between ED and decreased BRS ($r = 0.259$, $p = 0.159$). It could be explained by presence of different mechanisms responsible for alteration of endothelial and autonomic function in OSA. Although intermittent hypoxia could be the common initial mechanism, oxidative stress could be considered to be the most important mechanisms in the pathogenesis of ED, while modulation and adaptation of the baroreflex and chemoreflex activity could be more important in the genesis of decreased BRS (Victor *et al.* 2009; Freet *et al.* 2013).

This study has several limitations. Important limitation is the small sample size and absence of a control group. Selection of our study population can be seen as another limitation. We enrolled only subjects without any therapy or overt cardiovascular risk factors. Although selection probably helped to eliminate confounding from other associated conditions, enrolled subjects can deviate from common OSA patients with usual coexistence of several vascular risk factors. Bias could also be introduced by the fact that our cohort was a mixed population of male and female. Sex-related differences in the association between sleep-disordered breathing and endothelial function have been described previously (Faulx *et al.* 2004).

CONCLUSION

Results of our study support the association between severity of endothelial dysfunction and the severity of OSA described previously. In a population of patients with suspected OSA without any overt burden of cardiovascular risk factors, AHI seemed to be the only predictor of impaired endothelial function. Although both RHI and BRS were significantly decreased in the population with severe OSA, we failed to find any significant correlation between ED and impaired cardiovascular autonomic nervous system regulation. Nevertheless, OSA should be considered as an important vascular risk factor in a population without any overt burden of cardiovascular risk.

ACKNOWLEDGEMENTS

This work was supported by the Grant of The Ministry of Health of the Slovak Republic 2012/56-SAV-6 and by the Framework Programme for Research and Technology Development, Project: Building of Centre of Excellency for Sudden Cerebral Vascular Events, Comenius University Faculty of Medicine in Bratislava (ITMS:26240120023), cofinanced by European Regional Development Fund.

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